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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* HENG WANG and QILIANG CAI

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Appeal 2010-008569
Application 10/566,697
Technology Center 1600

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Before CAROL A. SPIEGEL, LORA M. GREEN, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for preparing polyepitope chimeric gene vaccines. The Patent Examiner rejected the claims on grounds of indefiniteness, anticipation, and

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm-in-part.

## STATEMENT OF THE CASE

"The method of the invention generally involves the construction of expression libraries of polyepitope chimeric genes with different sizes and lengths using gene shuffling and random assembly so as to screen polyepitope chimeric gene vaccines." (Spec. 1, ll. 7-10.) Claims 2, 3, 8, 9 and 13-25 are on appeal.[2] Claims 13 and 20 are representative and read as follows:

13. A method for preparing polyepitope chimeric gene vaccines, the method comprising the steps of:

a) selecting, synthesizing, and cloning into a vector a plurality of nucleic acid molecules each encoding a single epitope of an antigen of interest;

b) constructing nucleic acid molecules encoding randomly combined biepitopes in the vectors of step a) by isocaudamer linkage;

c) randomly assembling the nucleic acid molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths;

d) (i) isolating the polyepitope chimeric genes with different lengths into a plurality of different length ranges,

(ii) purifying and amplifying the isolated polyepitope chimeric genes,

(iii) subcloning the isolated polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries,

e) assessing the diversity of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries;

f) (i) immunizing animals with the polyepitope chimeric gene expression libraries to provide expression products of the genes;

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[2] Although dependent claims 4 and 10 were finally rejected, the Examiner's Answer did not maintain the rejections of these claims.

(ii) detecting the immunogenicity of the expression products of the genes;

g) selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope gene expression libraries and the immunogenicity of the expression products of the genes in the polyepitope gene expression libraries; and

h) screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines.

20. A method according to claim 19 [a method according to claim 13 wherein the expression libraries selected have immunological characteristics related to a predetermined antigen epitope] wherein the predetermined antigen epitope relates to a specific immunological type. (Text from claim 19 in brackets.)

The Examiner rejected the claims as follows:

- claim 20 under 35 U.S.C. § 112, 2nd paragraph, as indefinite;
- claims 2, 3, 8, 9 and 13-25 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over, Lin;[3] and
- claims 2, 3, 8, 9 and 13-25 under 35 U.S.C. § 103(a) as unpatentable over Sette[4] or Fikes,[5] either in view of Richards[6] or Applicants' admission of known prior art.

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[3] Lin Chengtao et al., *Construction of Malaria Multivalent Recombinant DNA Vaccine with Isocaudomer Technique*, 15 CHINESE J. BIOCHEM. AND MOL. BIOL. 974-977 (1999).

[4] Alessandro Sette et al., US 7,046,443 B1, filed Aug. 15, 2000, issued Apr. 11, 2006.

[5] John D. Fikes et al., US 6,602,510 B1, filed Apr. 5, 2000, issued Aug. 5, 2003.

[6] Cynthia Ann Richards et al., US 6,291,214 B1, issued Sep. 18, 2001.

## I. CLAIM 20 AND DEFINITENESS

*The Issue*

The Examiner's position is that the word "type" in claim 20 "renders the claims(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by 'type'), thereby rendering the scope of the claim(s) unascertainable." (Ans. 4.)

Appellants contend that "[t]he Examiner has failed to provide any factual support for her assertion that 'type' would not be reasonably apprised by the scope of the invention by the use of this term which has long been used in U.S. patent practice an[d] in fact appears in most patents." (App. Br. 14.) According to Appellants, the term "immunological type" appears in 54 issued U.S. patents, and "type" appears in 2,460,733 patents. (*Id.* at 15, n. 2.) Further, Appellants "are simply using a universally understood term of art in the field of immunology in the same sense as the term is conventionally used in the art." (Reply Br. 2.)

The issue with respect to this rejection is whether a person of ordinary skill in the art could determine whether a particular method infringes claim 20 or not.

*Findings of Fact*

1. The Specification states:

> Gene vaccines have many advantages compared to conventional vaccines, such as prolonged immune response, simultaneous induction of humoral immunity and cytotoxic T cell response, . . . . It not only has the safety proved by recombinant subunit vaccines and the high efficiency of attenuated virus vaccines for the induction of a general immune response but also *elicits specific types of immune response* in the body.
>
> (Spec. 2, ll. 16-23, emphasis added.)

2. The Specification indicates that the invention addresses certain DNA vaccine problems: "it is difficult to determine the quantity and linking order of the genes encoding polypeptides;" and "the induction of humoral immunity by epitope DNA vaccines is generally not satisfactory." (*Id.* at 4, ll. 22-26.)

3. The Specification states:

> The criteria to determine optimal assembly [of libraries] are based on the high diversity of the libraries and high immunogenicity of the expression products. In addition, the criteria may include the immunological characteristics related to the antigen epitopes of interest, *such as the specific immunological types and cytokines generated in the body elicited by the libraries tested* or the cross protective effects elicited in animal models.
>
> (*Id.* at 11, ll. 4-10, emphasis added.)

*Principles of Law*

> [T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification.

*In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

"A claim is indefinite if its legal scope is not clear enough that a person of ordinary skill in the art could determine whether a particular composition infringes or not." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003).

*Analysis*

Claim 20 limits the paragraph g) library selecting step by requiring that the predetermined epitope "relates to a specific immunological type."

According to the Specification, criteria for assembling an expression library may include characteristics related to the antigen epitopes of interest, "such as the specific immunological types and cytokines generated in the body elicited by the libraries tested." (FF3.) We agree with the Examiner that the Specification gives little if any enlightenment regarding "specific immunological types" generated by a body in response to antigens. The Specification also states that gene vaccines elicit "specific types of immune response" (FF1), but does not identify the "specific types" or explain what is meant.

Appellants contend that the Examiner failed to provide factual support for the rejection (App. Br. 14), but this contention is unpersuasive because the Examiner did provide factual support: there is no intrinsic evidence that a person of ordinary skill in the art would understand what "types" means. Appellants admit as much: "[t]he word 'type' is used but not defined in the specification." (Reply Br. 2.)

Appellants allude to conventional usage in the art. We agree that prior art references may be "indicative of what all those skilled in the art generally believe a certain term means ... [and] can often help to demonstrate how a disputed term is used by those skilled in the art," *Vitronics Corp. v. Conceptronic*, Inc., 90 F.3d 1576, 1584 (Fed. Cir. 1996), but Appellants have not provided extrinsic evidence meeting that criterion. For example, Appellants tell us that "the term 'immunological type' appears in 54 issued U.S. patents." (App. Br. 15, n. 2.) Although there is no evidence to support the allegation, we accept that the term may have appeared in 54 issued patents. However, Appellants provide no evidence showing how the term was used or what the term meant in those patents. The assumed fact of

appearance is not evidence establishing the meaning of the term, nor is it evidence that the 54 issued patents used the term in the same way or with a definite meaning. Next, Appellants assert that they "are simply using a universally understood term of art in the field of immunology in the same sense as the term is conventionally used in the art." (Reply Br. 2.) This argument is unpersuasive because it provides (i) no evidence that there is a universally understood conventional sense or meaning for the term, and (ii) no evidence showing sense or meaning.

Appellants have pointed to no intrinsic or extrinsic evidence in this record that clarifies what "specific immunological type" means, and we therefore find the Examiner has the better position. In the absence of pertinent evidence showing what "specific immunological types" means, we conclude that a person of ordinary skill in the art could not determine whether a particular method infringes claim 20.

## II. ANTICIPATION AND/OR OBVIOUSNESS OVER LIN

### *A. Anticipation by Lin*

*The Issue*

The Examiner's position is that Lin described making a chimeric multi-epitope *Plasmodium falciparum* DNA vaccine, and immunizing mice with the vaccine. (Final Rej. 10.) The Examiner found that "the specific method steps of Lin using specific components anticipates . . . the broad claimed method using broad components in the method." (*Id.*)

Appellants contend that "Lin does not identically disclose" the claimed invention and therefore did not anticipate. (App. Br. 15.) Appellants particularly dispute that Lin disclosed certain features in claim

13. (*Id.* at 15-16, listing disputed features.) The Examiner responds that "Lin discloses all the elements of the claim method using implicit terms for the claim term(s)." (Ans. 11.)

The issue with respect to the anticipation rejection is whether the evidence supports a finding that Lin implicitly disclosed all elements of the claimed method.

*Principle of Law*

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997) (citations omitted).

*Analysis*

We agree with the Examiner that Lin explicitly or implicitly disclosed a method comprising claimed steps a) and b), as well as cloning polyepitope chimeric genes into vectors, thus obtaining chimeric gene expression libraries, and immunizing animals with the chimeric gene expression libraries. However, we agree with Appellants that Lin did not explicitly describe a method comprising claim steps c) "randomly assembling the nucleic acid molecules" into chimeric genes, and d) including its three steps (i) through (iii). The Examiner found step c) and step d) implicit in Lin's disclosure, but did not identify evidence supporting the finding. It appears that Lin assembled its chimeric gene in an ordered way, rather than in a random way. *See* Lin's Fig. 1, illustrating part of the assembly, and Lin's text at part 2.1 describing the assembly. We therefore do not agree that Lin implicitly described Appellants' step c. In our review of Lin, we do not recognize evidence that Lin implicitly described step d), including its three steps (i) through (iii). We therefore must reverse the rejection.

*B. Obviousness Over Lin*

*The Issues*

The Examiner's position is that Lin described making a chimeric multi-epitope *Plasmodium falciparum* DNA vaccine, and immunizing mice with the vaccine. (Final Rej. 10.) The Examiner concluded that "the specific method steps of Lin using specific components . . . render[] obvious the broad claimed method using broad components in the method." (*Id.*)

Appellants dispute that Lin rendered the claimed invention obvious, arguing that there is no teaching, suggestion or motivation in Lin, inter alia:

> [i] to randomly assemble the nucleic acids molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths, nor
> [ii] to isolate the polyepitope chimeric genes into a plurality of different length ranges, nor
> [iii] to clone the polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, nor
> [iv] to assess the diversity of those libraries.

(App. Br. 17, bracketed letters added.) The Examiner responds that "[i]t would have been obvious to separate the different epitopes of different length into separate length ranges (sizes), as appellants recognize at [Specification] page 10, lines 22-23, 'one skilled in the art may set any desired length ranges.'" (Ans. 13.) Further, the Examiner responds that "[i]t would also be within the ordinary skill in the art to ascertain termination of the reiterative step of recloning (rescreening) of a pool (library) of epitopes when the desire[d] immunogenicity of the polyepitope is obtained." (*Id.*)

The issues with respect to the obviousness rejection are:

[i] did Lin describe randomly assembling polyepitope chimeric genes with different lengths, and if not, has the Examiner identified a reason to do so;

[ii] did Lin describe isolating polyepitope genes into a plurality of different length ranges, and if not, has the Examiner identified a reason to do so;

[iii] did Lin describe cloning polyepitope chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, and if not, did the Examiner identify a reason to do so; and

[iv] did Lin describe assessing the diversity of the polyepitope gene expression libraries, and if not, did the Examiner identify a reason to do so?

*Principles of Law*

When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention – including all its limitations – with the teachings of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995). "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006), cited with approval in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

*Analysis*

Concerning issue [i], we have already found that Lin appears to have described assembling its chimeric gene in an ordered, rather than random way. *See* Anticipation section above. The rejection does not articulate reasoning showing that a person of ordinary skill in the art would have wanted to change to a random assembly method.

Concerning issue [ii], the Examiner has not pointed to evidence showing that Lin described isolating polyepitope genes into a plurality of

different length ranges. We do not dispute the Examiner's finding that a person of ordinary skill in the art could have done so if they wished, but the rejection assumes there would have been a reason to do so. Although a rejection for obviousness does not have to identify an explicit suggestion, motivation, or teaching to alter a prior art method, it must still identify a reason to do so that would have derived from a source other than the Appellants' Specification.

Without a basis for plural length genes generated by step d)'s isolating step to have been obvious, there is no basis for concluding that the following steps in the method using the plural length genes to generate plural libraries would have been obvious. In other words, the rejection's foundation for reaching issues [iii] and [iv] is lacking. We therefore agree with Appellants that the rejection for obviousness over Lin must be reversed.

## III. OBVIOUSNESS OVER THE COMBINED TEACHINGS OF SETTE OR FIKES, IN VIEW OF RICHARDS OR ADMITTED PRIOR ART

*The Issue*

The Examiner's position is that each of Sette and Fikes described a method of making polyepitope gene vaccines, but that neither taught using isocaudamer linkage. (Ans. 5-7.) The Examiner found that Richards taught (1) using isocaudamer restriction enzymes to link fragments into a cDNA and clone it into a vector for a library, and (2) efficiency gains from using the isocaudamer procedure. (*Id.* at 7-8.) The Examiner also found that Appellants' Specification disclosed that "[v]arious isocaudamers are known in the art." (*Id.* at 8, citing Spec. 10, ll. 5-6.) The Examiner concluded that

it would have been obvious "to use isocaudamer linkage in the method of either Sette or Fikes for the advantages taught by Richards." (*Id.*)

Appellants contend there is nothing in any combination of the references which would teach, suggest, or motivate constructing molecules encoding randomly combined bi-epitopes, or that such molecules should be randomly assembled into polyepitope chimeric genes with different lengths, or that the polyepitope chimeric genes with different lengths be isolated into a plurality of different length ranges, purified, amplified and subcloned into expression vectors to obtain libraries, or that the diversity or immunogenicity of the plural libraries should be assessed, or that the results be employed in selecting a library for further screening to identify gene clones for use as vaccines. (App. Br. 19-20.) According to Appellants, Sette made no attempt to randomize the sequence of epitopes within the construct, and did not recognize that the sequence could have an effect on the immunogenicity. (*Id.* at 20.) Appellants argue that Fikes likewise "fail to disclose randomizing the sequence of the epitopes in the construct and screening for optimized immunogenicity." (*Id.*) Although Appellants agree that isocaudamers are a well-known linkage technique, they conclude their argument as follows: "[t]he combination of Sette et al. or Fikes et al. with Richards or the allegedly admitted prior art would at most teach or suggest the first two of the eight steps of independent claim 13 . . . ." (*Id.* at 24.)

The issue with respect to this rejection is whether Sette or Fikes provided a reason to randomize the sequence of epitopes in a chimeric gene, isolate chimeric genes into a plurality of different lengths to be purified, amplified and subcloned into expression vectors to obtain libraries, and carry out the other steps in the claimed method.

*Analysis*

We agree with the Examiner's finding that the efficiency advantages taught by Richards were a suggestion to use isocaudamer linkage in the methods of Sette or Fikes. However, we agree with Appellants that neither Sette nor Fikes taught or suggested randomly combining bi-epitopes as recited in claim 13, step b). The Examiner cites Sette's Example 10 as disclosing randomization (Ans. 15-16), but we find no mention of randomization in the cited passages. In responding to Appellants' argument that Fikes did not disclose or suggest randomizing, the Examiner states "please see the responses above under Sette." (*Id.* at 16.) The rejection on appeal stated that the claims were rejected over Sette *or* Fikes, and the reference to Sette's Example 10 does not explain how Fikes independently taught or suggested randomization.

Appellants have alleged multiple differences between claim 13's method and those of Sette and Fikes, in addition to the randomization feature. Although the rejection included several block quotes from Sette and Fikes, the quoted passages do not appear to explicitly disclose all the steps in claim 13. Because the rejection did not account for all the differences between claim 13 and the prior art, we must reverse it.

## CONCLUSIONS

A person of ordinary skill in the art could not determine whether a particular method infringes claim 20.

The evidence does not support finding that Lin implicitly disclosed all elements of the claimed method.

The evidence does not support finding that Lin described randomly assembling polyepitope chimeric genes with different lengths, and the rejection did not show there would have been a reason to do so.

The evidence does not support finding that Lin described isolating polyepitope genes into a plurality of different length ranges, and the rejection did not show there would have been a reason to do so.

The evidence does not support finding that Sette or Fikes provided a reason to randomize the sequence of epitopes in a chimeric gene.

## SUMMARY

We affirm the rejection of claim 20 under 35 U.S.C. § 112, 2nd paragraph.

We reverse the rejection of claims 2, 3, 8, 9 and 13-25 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over, Lin.

We reverse the rejection of claims 2, 3, 8, 9 and 13-25 under 35 U.S.C. § 103(a) as unpatentable over Sette or Fikes, in view of Richards or Applicants' admission of known prior art.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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